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1-Aminoalkanephosphonic acids. Addition of diethyl phosphite to *N*-diisobutylaluminio-aldimines

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Abstract

A new route to 1-aminoalkanephosphonic acids starting from nitriles has been elaborated. The nitriles are reduced by Dibal–H into imine derivatives; addition with diethyl phosphite gives the corresponding 1-aminoalkanephosphonates. Hydrolysis of latter compounds gives the 1-aminoalkanephosphonic acids.

Introduction

Although a number of routes to 1-aminoalkanephosphonic acids **1** have been developed during the last decade [1,2], in light of the discovery that peptides containing **1** possess interesting biological properties [3,4,5], new procedures to make **1** are still desirable.

This requirement is particularly relevant in the synthesis of functionalized 1-aminoalkanophosphonates, for which the general procedures described cannot always be used.

The ready access to organic compounds bearing nitrile and another functional group inside the same molecule affords new possibilities for the preparation of new 1-aminoalkanephosphonic acids. Thus, the higher stability of cyano compared to that of the carbonyl function facilities the synthesis of aminoalkanophosphonates **1**, especially when the aldehyde substrates for **1** are unstable in the free form (e.g. **6h**), or when prepared from corresponding nitrile derivatives [6].

Here we describe the simple route to **1** which consists in the addition of diethyl phosphite (**8**) to *N*-diisobutyloaluminio-imines (**4**). The latter compounds are prepared by reaction of alkyl (aryl) nitriles (**5**) with diisobutyloaluminiumhydride (Dibal–H) (**7**) and without prior isolation are subjected to reaction with **8**. Subsequent reaction of the intermediates **3** (see Scheme 1) with acetic acid, followed treatment with hydrochloric acid gives **1** which are isolated by standard methods (see Table 1) [7*].

* Reference number with asterisk indicates a note in the list of references.

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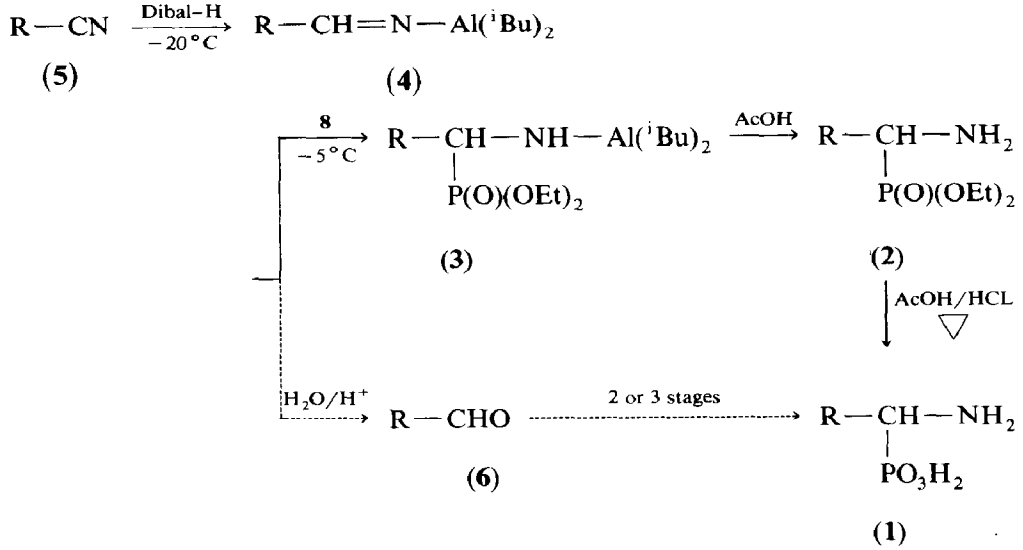
Table 1. Yields and physical characteristics of 1-aminoalkanephosphonic acids **1**

	R	Yield [a] (%)	Mp (°C)	TLC (R_f)	^{31}P NMR δ (ppm)	^{1}H NMR [i] δ (ppm)
1a	CH_3	48	274–276 (270–273) [8] (272–274) [10]	0.21 [d] 0.47 [e]	17.8 [f] 22.0 [g]	
1b	C_2H_5	47	265–267 (261–265) [8] (262–264) [11]	0.27 [d] 0.51 [e]	17.6 [f] 21.4 [g]	
1c	n-C_3H_7	57	262–263 (263–265) [8] (262–264) [11]	0.40 [d] 0.55 [e]	17.2 [f] 21.7 [g]	
1d	n-C_4H_9	51	263–266 (260–263) [10]	0.51 [d] 0.57 [e]	17.8 [f] 21.7 [g]	
1e	C_6H_5	62	270–272 (279–281) [8] (269–271) [11]	0.49 [d] 0.56 [e]	13.9 [f] 17.6 [g]	
1f	$C_6H_5CH_2$	70	263–265 (272–274) [8] (267–269) [11]	0.45 [d] 0.64 [e]	14.9 [f] 20.0 [g]	
1g	CH_2=$CHCH_2$	33	244–246 [b]	0.37 [d] 0.50 [e]	15.71 [f] 20.14 [g]	2.1–3.2(m,2H,CH_2CHN);3.5–4.2(m,1H,CHN); 5.1–5.6(m,2H,CH_2=CH);5.6–6.2(m,1H,CH_2=CH);6.6–7.9(m,3H,NH_3)
1h	FCH_2	33	191–195 [b,c]	0.17 [d]	10.5 [h] 16.1 [g]	3.7–4.1(m,2H,FCH_2);4.6–5.0 (m,1H,CH)

[a] Conditions were not optimized. Yields are relative to starting nitrile. [b] Microanalysis data of new compounds (**1g** and **1h**) were in satisfactory agreement with calculated values: ***1g***: Found: C, 31.14; H, 6.44; N, 8.60; P, 20.07. $C_4H_{10}NPO_3 \cdot 0.25\ H_2O$ calc: C, 30.80; H, 6.43; N, 9.00; P, 19.91%. ***1h***: Found: C, 16.91; H, 5.04; N, 9.39; P, 21.91. $C_2H_7FNPO_3$ calc: C, 16.78; H, 4.90; N, 9.79; P, 21.68%. [c] 1-Amino-2-fluoroethylphosphonic acid (**1h**) have been recently reported by Flynn [10] but no analytical data for **1h** were given. [d] R_f values measured by TLC on cellulose plates DC (E. Merck), eluent: n-butanol/acetic acid/water (12:3:5). Indicator: 0.5% ninhydrin in ethanol. [e] As above; eluent: isopropanol/ammonia (25% aq)/water (7:1:1). [f] ca. 5% solution in CF_3COOH. [g] 5% in 2 *N* KOH. [h] 5% in 3 *N* HCl. [i] Solution in CF_3COOH (**1g**) or in mixture of CF_3COOH/D_2O (1:2) (**1h**)

Our one-pot procedure gives the desired amino acids **1** in moderate to good yields and can be regarded as a good alternative to the previously published procedures of Gancarz and Wieczorek [8], and Kotynski and Stec [9] in which organic nitriles were used as substrates to prepare **1**. Note that in both stages the conversion of nitrile to aldimine **4** and the addition of diethyl phosphite (**8**) to intermediary **3** occurs under mild conditions, in the presence of a small excess of **8**.



Experimental

All melting points were measured on Boetius apparatus and are uncorrected. ^{31}P NMR spectra were recorded on a JEOL C-60H spectrometer equipped with the Heterospin Decoupler SNH–SP–HC at 24.3 MHz with external H_3PO_4 as reference. Negative chemical shift values are reported for compounds that absorb at higher fields than H_3PO_4. ^1H NMR spectra were recorded at 80 MHz on a Tesla BS-487 spectrometer. Product purities were determined from the integrated NMR spectra, and by chromatography on cellulose plates (TLC). The diisobutylaluminiumhydride (Dibal–H), the nitriles, and the diethyl phosphite were commercial products.

Preparation of 1-aminoalkanephosphonic acids (1)

To the solution of the relevant alkyl (aryl) nitrile (20 mmole, freshly distilled over CaH_2) in dry diethyl ether (5 ml), under argon, was added dropwise under argon, at −20 °C, diisobutylaluminiumhydride (20 mmole, 20 ml of 1 *M* solution in hexane). The mixture was stirred for 1 h, and then diethyl phosphite (50 mmole, 6,9 g) in diethyl ether (10 ml) was added at between −5 and 0 °C. After 3 h stirring at room temperature, acetic acid (25 ml) was carefully added and the reaction mixture was evaporated under reduced pressure (20 mmHg and 0.3 mmHg) in a bath at 60 °C. The oily residue was dissolved in acetic acid (25 ml) and hydrochloric acid (36% aq., 40 ml) and the solution was refluxed for 7 h. The solvents were evaporated under reduced pressure, the solid residue was dissolved in water (10 ml), and this solution was passed through ion exchanger (Dowex 50W × 2 or Dowex 1 × 2) column. The

fractions containing **1** (ninhydrin test) were collected and concentrated. Aminoalkanephosphonic acids **1** were precipitated with ethanol, filtered off and dried under reduced pressure in a desiccator over P_2O_5. The analytical data and yields (not optimized) are listed in Table 1.

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